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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| **APPLICANT:** | Wilfred H. Nelson et al. | **GROUP:** | 1641 |
| **SERIAL NO:** | 08/818,534 | **EXAMINER:** | J. Hines |
| **FILED:** | 03/14/97 | | |
| **FOR:** | **DIRECT DETECTION OF BACTERIA-ANTIBODY COMPLEXES VIA UV RESONANCE RAMAN SPECTROSCOPY** | | |

**Assistant Commissioner of Patents**
**Washington, D.C. 20231**

**Sir:**

**PRELIMINARY AMENDMENT**

The Office Action of March 20, 2000 has been received and the comment of the Examiner carefully considered.

Claims 2, and 9-12 have been rejected. Claims 2, and 9-12 remain in prosecution. No new matter has been added.

The objections and the rejections shall be taken up in the order presented in the Office Action.

**5.** The Examiner has rejected claims 2, 9 and 12 pursuant to 35 U.S.C. §103 as being obvious in view of Nelson et al. (U.S. Pat. No. 4,487,198) and Herron et al. Nelson et al. discloses a method for identifying bacteria using resonance enhanced Raman backscattered energy spectra. Herron et al. is cited by the Examiner as evidence that immobilizing bacteria using antibodies is well known in the art as a method of immobilization. The Examiner contends that it would have been obvious to modify the method disclosed in Nelson et al. with the

knowledge generally available to one of ordinary skill in regard to immobilizing bacteria using antibodies to produce Applicant's claimed invention.

Applicant claims a method for detecting the presence of a specific microorganism in a sample comprising contacting the sample with a medium having solid phase immobilized antibodies which specifically bind to a characteristic cell surface antigen of a microorganism to form an immobilized antigen-antibody complex, irradiating the medium with laser light of 242-257nm to produce a resonance enhanced Raman backscattered energy spectrum, and comparing the results of the induced spectrum with known spectrum correlated with previously identified microorganisms to detect the presence of a specific microorganism in the sample, **the sample being comprised of at least 200 fold antibodies.** (emphasis added).

The Examiner's obviousness rejection is improper because there is no reasonable expectation of success to modify the prior art as proposed by the Examiner to produce Applicant's claimed invention. The prior art can not be modified or combined to reject claims as *prima facie* obvious unless there is a **reasonable expectation of success.** (emphasis added) In re Merck & Co., Inc., 800 F.2d 1091 (Fed. Cir. 1986). The Examiner assumes that because it was known in the art to immobilize bacteria using antibodies in a bacterial assay that one of ordinary skill in the art would have modified the method disclosed in Nelson et al., which identifies bacteria using resonance enhanced Raman backscattered energy spectra, to produce Applicant's claimed invention with a reasonable expectation of success. However, Applicant unexpectedly discovered that irradiating antibody molecules bound to antigens of the microorganisms does not produce resonance Raman spectra which interferes with the resonance Raman spectra of the irradiated microorganisms. See specification at the bottom of page 3 bridging to the top of page 4. The discovery that irradiating antibody molecules bound to antigens of the microorganisms

did not produce resonance Raman spectra which interfered with the resonance Raman spectra of the irradiated microorganisms enables the detection of a minute number of bacteria in the presence of a large number of antibodies thereby providing a highly sensitive and efficient method of detection. See specification at the middle of page 5 and the middle of page 7.

In the absence of a teaching in the prior art which would suggest that the irradiation of antibodies would not interfere with the resonance Raman spectra of targeted irradiated microorganisms in an assay, one of ordinary skill in the art would not combine the known method of immobilizing bacteria using antibodies and the method of identifying bacteria using resonance enhanced Raman backscattered energy spectra with a reasonable expectation of success. Herron et al. does not even remotely teach or suggest that the irradiation of the antibodies used to immobilize the bacteria of interest in an analyte would produce resonance Raman spectra that would not obscure the resonance Raman spectra produced by the irradiated bacteria of interest. Therefore, Applicant respectfully requests that the Examiner's obviousness rejection of claims 2, 9 and 12 be withdrawn.

**6.** The Examiner has rejected claims 2 and 9-12 as being obvious pursuant to 35 U.S.C. §103 in view of Chadha et al. and Herron et al. Chadha et al. teaches the resonance enhancement of the vibrational modes of bacteria by UV excitement. Applicant respectfully submits that the obviousness rejection has been traversed because one of ordinary skill in the art would not modify Chadha et al. and the known method of immobilizing bacteria of interest in an analyte, i.e. by substituting biospecific antibodies for the disclosed polylysine in Chadha, to produce Applicant's claimed invention with a reasonable expectation of success for the same reasons argued *supra*.

Applicant argues that the Examiner's obviousness rejections pursuant to enumerated paragraphs **5** and **6** are improper because the Examiner has failed to consider the invention as whole in view of the cited art. In regard to the positive limitation of independent claim 9 which recites, "**...the sample being comprised of at least 200 fold antibodies.**"(emphasis added), the Examiner contends that because it is well-known in the art to immobilize bacteria using antibodies in an assay, "no more than routine skill is involved in adjusting the amount of a component of a claimed process to suit a particular starting material in order to achieve the results taught in the prior art" or "changes in concentrations or the amount of antibody for a process known in the art does not impart patentability". See office action enumerated paragraphs **5** and **6**.

The Applicant is not solely claiming a process of detecting bacteria in an analyte by immobilizing bacteria using antibody-antigen complexes. Applicant is claiming a process of detecting microorganisms in a sample by not only immobilizing the microorganisms using antibody-antigen complexes but also by irradiating the complexes with light to produce resonance Raman spectra wherein the antibodies of the complexes **unexpectedly do not obscure the resonance Raman spectra produced by the microorganisms.** Further, as the concentration of the antibodies is increased, the irradiation of the greater concentration of antibodies **unexpectedly** does not produce resonance Raman spectra which appreciably interferes with the resonance Raman spectra of the microorganisms of interest. Therefore, Applicant respectfully requests that the Examiner withdraw the obviousness rejections of claims 2 and 9-12, as claims 2 and 10-12 are dependent on claim 9, because the Examiner fails to consider the invention as a whole in view of the cited art, particularly in regard to the limitation of claim 9.

Further, Applicant hereby submits supplemental evidence for the record in the form of a preprint of a peer review paper that supports Applicant's assertion that the claimed method, which allows for the detection of bacteria in the presence of a high antibody/antigen ratio, is not obvious in view of the combined prior art. The enclosed peer review paper establishes that the claimed method is sensitive enough as to detect bacteria in an analyte having an antibody/bacterium ratio of 1,000,000 to 1. See enclosed peer review paper at page 14, first paragraph which discloses that no resonance Raman spectra interference is observed at 251 nm excitation at an antibody/bacterium ratio of $10^6/1$. One of ordinary skill in the art clearly would not have had a reasonable expectation of success to combine the prior art references to produce such a sensitive method, as now claimed, for detecting the presence of a microorganism in an analyte whereby at least 200 fold antibody molecules in excess of the target antigen can be introduced into the analyte without affecting the means for detecting the microorganism.

It is submitted that the claims are in condition for allowance and notification of the same is earnestly solicited.

Respectfully submitted

Richard L. Stevens
Registration No. 24,445
Samuels, Gauthier & Stevens
225 Franklin Street, Suite 3300
Boston, Massachusetts 02110
Telephone: (617) 426-9180
Extension 122